PATENT
CASE IN0291K2GQ1B1C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
BISHOP ET AL.	Examiner: To Be Assigned
For Patent For: TRICYCLIC AMIDE AND UREA COMPOUNDS USEFUL FOR INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT OF PROLIFERATIVE DISEASES	Group: To Be Assigned Date: December 20, 2001
Serial No.: To Be Assigned	Prior Examiner: T. Truong
Filed: Herewith	Prior Group: 1624
Related To: This is a diviskional of Application Serial No. 09/350,870 filed July 9, 1999	

Schering-Plough Corporation
Kenilworth, New Jersey 07033-0530

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

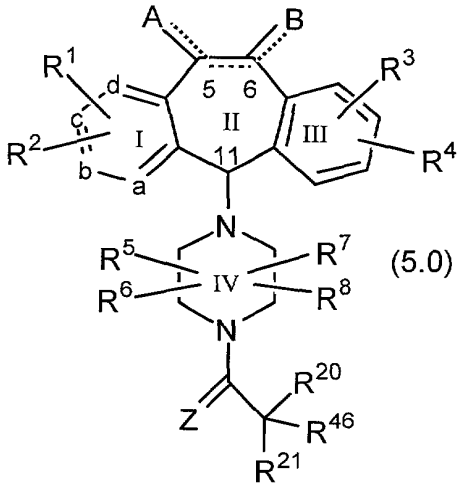
Please amend the above identified application as follows:

IN THE CLAIMS

Cancel Claims 1-12, and 22-27 without prejudice.

Replace Claim 13 with the like numbered claim below.

13. (AMENDED) A compound selected from a compound of the formula:



(5.0)

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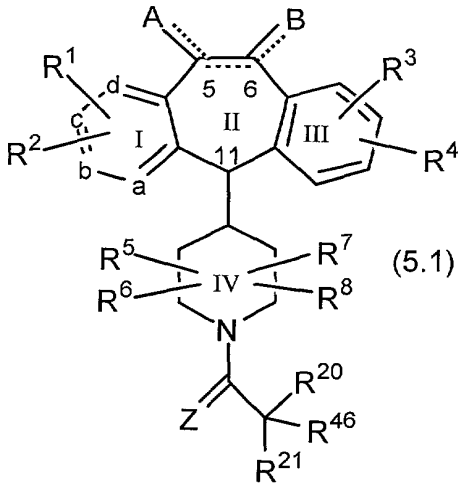

(5.1)

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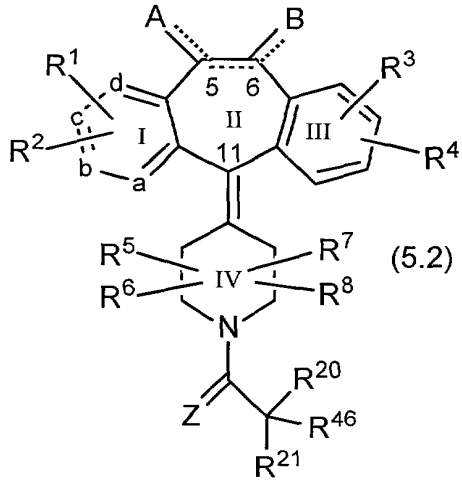

(5.2)

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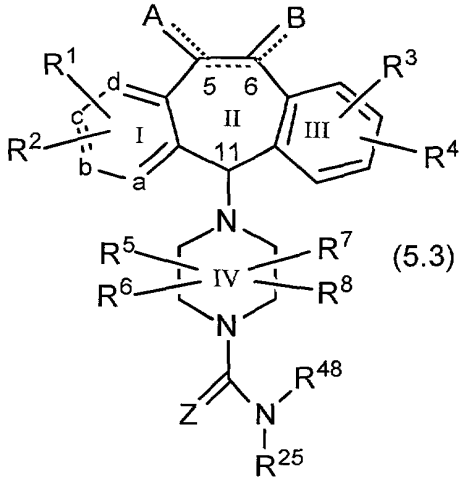

(5.3)

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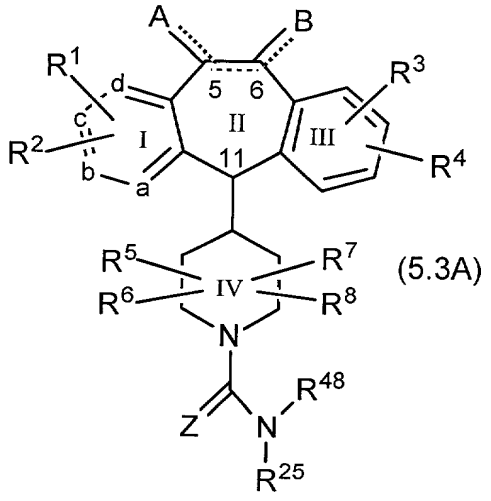
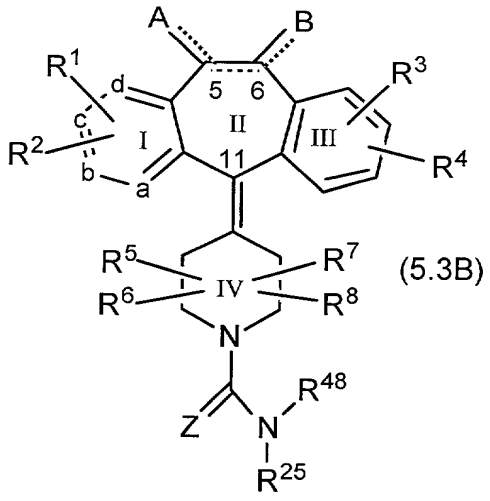


(5.3A)

or



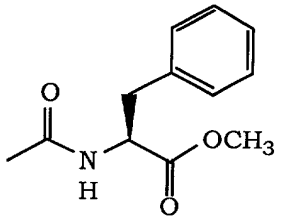
(5.3B)

or a pharmaceutically acceptable salt or solvate thereof, wherein :

one of a, b, c and d represents N or NR^9 wherein R^9 is O^-, $-CH_3$ or $-(CH_2)_nCO_2H$ wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2;

each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2), -SCN, $-N(R^{10})_2$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$,



,

$-SR^{11}N(R^{75})_2$ (wherein each R^{75} is independently selected from H and $-C(O)OR^{11}$), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring;

R^5, R^6, R^7 and R^8 each independently represents H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{10}$,

$-SR^{10}$, $-S(O)_tR^{11}$, $-NR^{10}COOR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{11}$, $-CO_2R^{10}$, OPO_3R^{10} or one of R^5, R^6, R^7 and R^8 can be taken in combination with R^{40} as defined below to represent $-(CH_2)_r-$ wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, $-CF_3$ or aryl, or R^5 is combined with R^6 to represent =O or =S and/or R^7 is combined with R^8 to represent =O or =S;

R^{10} represents H, alkyl, aryl, or aralkyl;

R^{11} represents alkyl or aryl;

X represents N, CH or C, which C may contain an optional double bond, represented by the dotted line, to carbon atom 11;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{11})_2$; H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{10}$, H and $-OR^{10}$, =O, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4;

R^{20}, R^{21} and R^{46} are each independently selected from the group consisting of:

(1) H;

(2) $-(CH_2)_qSC(O)CH_3$ wherein q is 1 to 3;

(3) $-(CH_2)_qOSO_2CH_3$ wherein q is 1 to 3;

(4) -OH;

(5) $-CS(CH_2)_w$(substituted phenyl) wherein w is 1 to 3 and the substitutents on said substituted phenyl group are the same substitutents as described below for said substituted phenyl;

(6) $-NH_2$;

(7) -NHCBZ;

(8) $-NHC(O)OR^{22}$ wherein R^{22} is an alkyl group having from 1 to 5 carbon atoms, or R^{22} represents phenyl substituted with 1 to 3 alkyl groups;

(9) alkyl;

(10) $-(CH_2)_k$phenyl wherein k is 1 to 6;

(11) phenyl;

(12) substituted phenyl wherein the substituents are selected from the group consisting of: halo, NO_2, -OH, $-OCH_3$, $-NH_2$, $-NHR^{22}$, $-N(R^{22})_2$,

alkyl, -O(CH_2)$_t$phenyl (wherein t is from 1 to 3), and -O(CH_2)$_t$substituted phenyl (wherein t is from 1 to 3);

(13) naphthyl;

(14) substituted naphthyl, wherein the substituents are as defined for substituted phenyl above;

(15) bridged polycyclic hydrocarbons having from 5 to 10 carbon atoms;

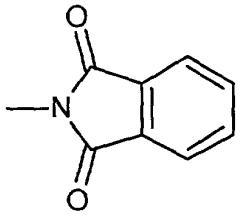
(16) cycloalkyl having from 5 to 7 carbon atoms;

(17) heteroaryl;

(18) hydroxyalkyl;

(19) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidinyl, 1-(4-methylpiperazinyl), -S(O)$_t$R^{11}, or any of the substituents given above for said substituted phenyl, and said substitutents are bound to a ring carbon by replacement of the hydrogen bound to said carbon;

(20) (21) (22)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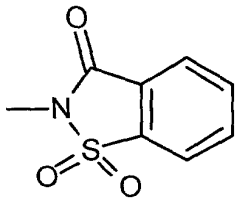
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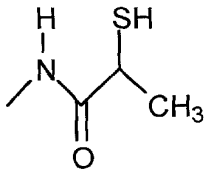
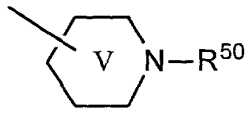

;

(23) -NHC(O)-(CH_2)$_k$-phenyl or -NH(O)-(CH_2)$_k$-substitued phenyl, wherein said k is as defined above;

(24) piperidine Ring V:

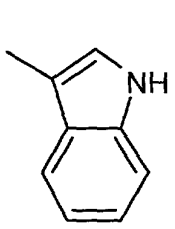

,

wherein R^{50} represents H, alkyl, alkylcarbonyl, alkyloxycarbonyl, haloalkyl, or -C(O)NH(R^{10}) wherein R^{10} is H or alkyl;

(25) -NHC(O)$CH_2C_6H_5$ or -NHC(O)CH_2-substituted-C_6H_5;

(26) -NHC(O)OC_6H_5;

(27) (28) (29)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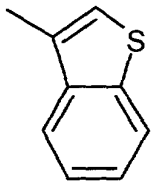
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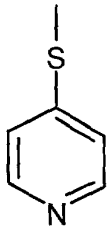
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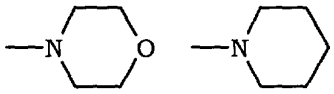
(30) -OC(O)-heteroaryl;

(31) -O-alkyl; and

(32) $-CF_3$;

(33) -CN;

(34) a heterocycloalkyl group of the formula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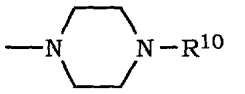
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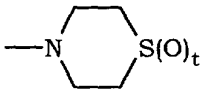
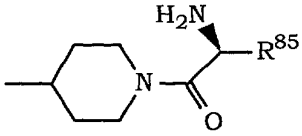

; and

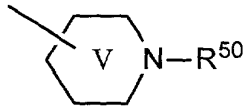
(35) a piperidinyl group of the formula



wherein R^{85} is H, alkyl, or alkyl substituted by -OH or $-SCH_3$; or

R^{20} and R^{21} taken together form a =O group and the remaining R^{46} is as defined above; or

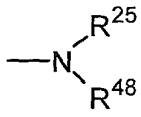
Two of R^{20}, R^{21} and R^{46} taken together form piperidine Ring V


,

wherein R^{50} is as defined above;

with the proviso that R^{46}, R^{20} and R^{21} are selected such that the carbon atom to which they are bound does not contain more than one heteroatom;

R^{44} represents



wherein R^{25} represents heteroaryl, N-methylpiperdinyl or aryl; and R^{48} represents H or alkyl;

Z represents O or S; and

wherein for the compounds of Formula 5.2 the substituents R^{20}, R^{21}, and R^{46} are selected such that when one of said substituents R^{20}, R^{21}, and R^{46} is selected from the group consisting of: (1) H, (4) -OH, (6) $-NH_2$, (8) $-NHC(O)OR^{22}$, (9) alkyl, (11) phenyl, (17) heteroaryl, (18) hydroxyalkyl, (19) substituted pyridyl, (12) substituted phenyl and (31) -O-alkyl, then the remaining two of said substituents R^{20}, R^{21} and R^{46} cannot both be H when: (a) R^1 and R^2 are both H, and (b) the double bond between C-5 and C-6 is absent, and (c) both A and B are H_2, and (d) R^4 is H, and (e) R^3 is H or Cl at C-8.

IN THE SPECIFICATION

On page 1, below the title, insert:

"REFERENCE TO RELATED APPLICATIONS

This is a divisional of Application Serial No. 09/350,870 filed July 9, 1999, which in turn is a continuation of Application Serial No. 08/971,038 filed November 14, 1997 (now abandoned), which in turn is a division of Application Serial No. 08/450,288 filed May 25, 1995 (now U.S. 5,696,121), which in turn is a continuation of Application Serial No. 08/410,187 filed March 24, 1995 (now U.S. 5,719,148), which in turn is a continuation-in-part of Application Serial No. 08/312,028 filed September 26, 1994 (now abandoned), which in turn is a continuation-in-part of Application Serial No. 08/137,862 filed October 15, 1993 (now abandoned)."

REMARKS

The amendments to Claim 13 incorporate the limitations of cancelled Claim 1.

Claims 13-21 remain in the Application.

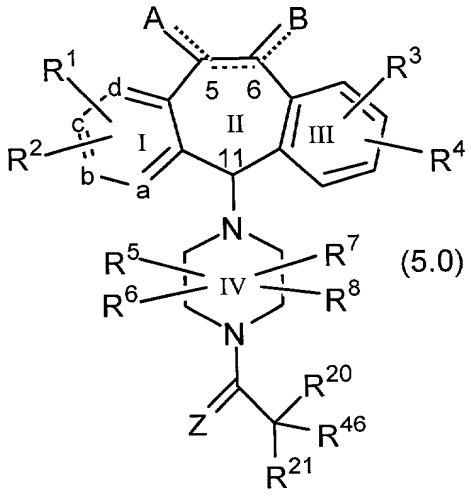
Respectfully submitted,

Henry C. Jeanette
Reg. No. 30, 856
Attorney for Applicants
(908) 298-5041

Doc. No. 21336v1

Claim Showing Amendments Made

13. (AMENDED) A compound selected from a compound of the formula: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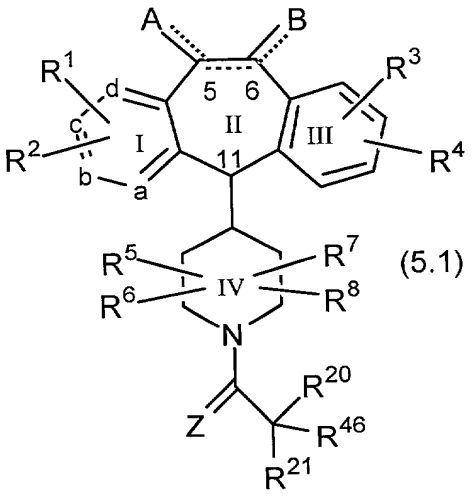
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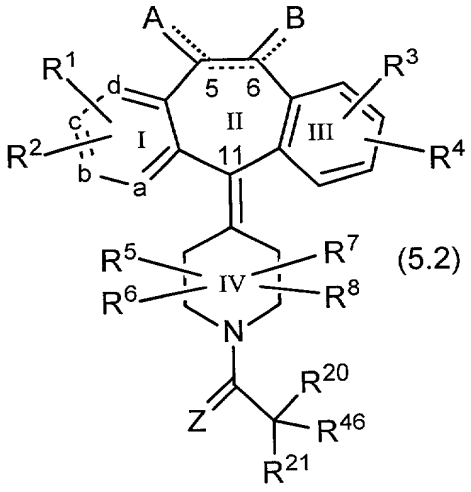
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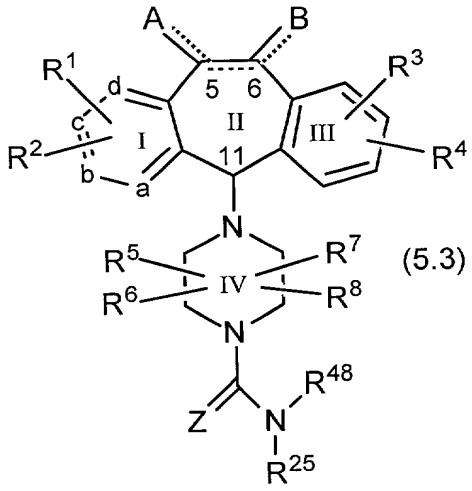
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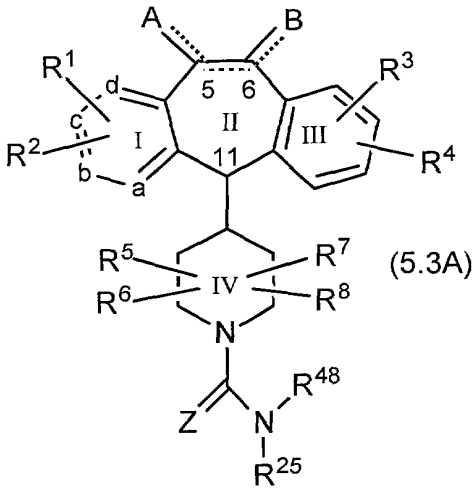
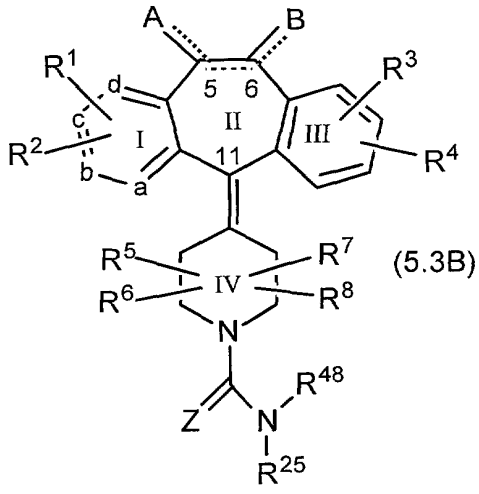




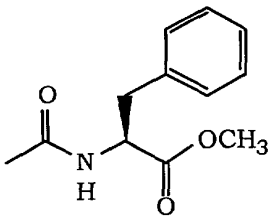
or

or a pharmaceutically acceptable salt or solvate thereof, wherein :

one of a, b, c and d represents N or NR^9 wherein R^9 is O^-, $-CH_3$ or $-(CH_2)_nCO_2H$ wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2;

each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2), -SCN, $-N(R^{10})_2$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$,



$-SR^{11}N(R^{75})_2$ (wherein each R^{75} is independently selected from H and $-C(O)OR^{11}$), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring;

R^5, R^6, R^7 and R^8 each independently represents H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{10}$,

$-SR^{10}$, $-S(O)_tR^{11}$, $-NR^{10}COOR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{11}$, $-CO_2R^{10}$, OPO_3R^{10} or one of R^5, R^6, R^7 and R^8 can be taken in combination with R^{40} as defined below to represent $-(CH_2)_r-$ wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, $-CF_3$ or aryl, or R^5 is combined with R^6 to represent =O or =S and/or R^7 is combined with R^8 to represent =O or =S;

R^{10} represents H, alkyl, aryl, or aralkyl;

R^{11} represents alkyl or aryl;

X represents N, CH or C, which C may contain an optional double bond, represented by the dotted line, to carbon atom 11;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{11})_2$; H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{10}$, H and $-OR^{10}$, =O, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4;

R^{20}, R^{21} and R^{46} are each independently selected from the group consisting of:

(1) H;

(2) $-(CH_2)_qSC(O)CH_3$ wherein q is 1 to 3;

(3) $-(CH_2)_qOSO_2CH_3$ wherein q is 1 to 3;

(4) -OH;

(5) $-CS(CH_2)_w$(substituted phenyl) wherein w is 1 to 3 and the substitutents on said substituted phenyl group are the same substitutents as described below for said substituted phenyl;

(6) $-NH_2$;

(7) -NHCBZ;

(8) $-NHC(O)OR^{22}$ wherein R^{22} is an alkyl group having from 1 to 5 carbon atoms, or R^{22} represents phenyl substituted with 1 to 3 alkyl groups;

(9) alkyl;

(10) $-(CH_2)_k$phenyl wherein k is 1 to 6;

(11) phenyl;

(12) substituted phenyl wherein the substituents are selected from the group consisting of: halo, NO_2, -OH, $-OCH_3$, $-NH_2$, $-NHR^{22}$, $-N(R^{22})_2$,

alkyl, -O(CH_2)$_t$phenyl (wherein t is from 1 to 3), and -O(CH_2)$_t$substituted phenyl (wherein t is from 1 to 3);

(13) naphthyl;

(14) substituted naphthyl, wherein the substituents are as defined for substituted phenyl above;

(15) bridged polycyclic hydrocarbons having from 5 to 10 carbon atoms;

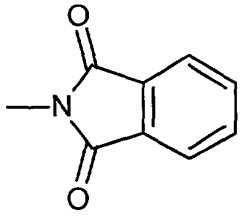
(16) cycloalkyl having from 5 to 7 carbon atoms;

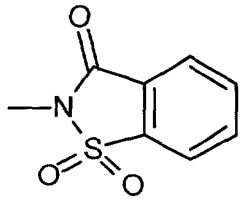
(17) heteroaryl;

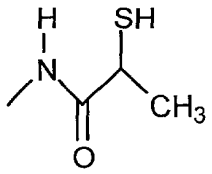
(18) hydroxyalkyl;

(19) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidinyl, 1-(4-methylpiperazinyl), -S(O)$_t$$R^{11}$, or any of the substituents given above for said substituted phenyl, and said substitutents are bound to a ring carbon by replacement of the hydrogen bound to said carbon;

(20) (21) (22)

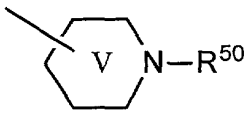






(23) -NHC(O)-(CH_2)$_k$-phenyl or -NH(O)-(CH_2)$_k$-substitued phenyl, wherein said k is as defined above;

(24) piperidine Ring V:

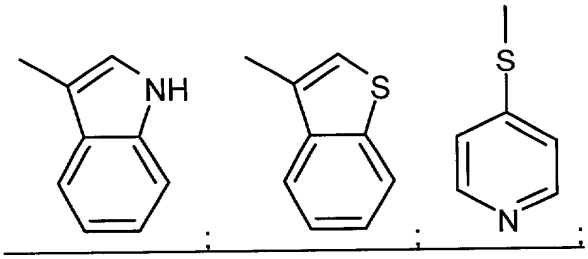


wherein R^{50} represents H, alkyl, alkylcarbonyl, alkyloxycarbonyl, haloalkyl, or -C(O)NH(R^{10}) wherein R^{10} is H or alkyl;

(25) -NHC(O)$CH_2C_6H_5$ or -NHC(O)CH_2-substituted-C_6H_5;

(26) -NHC(O)OC_6H_5;

(27) (28) (29)



;

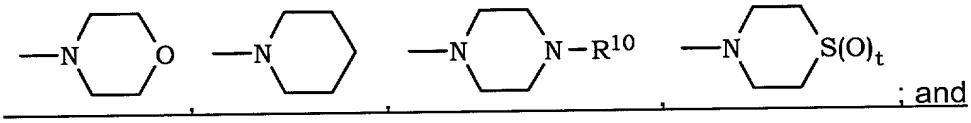
(30) -OC(O)-heteroaryl;

(31) -O-alkyl; and

(32) $-CF_3$;

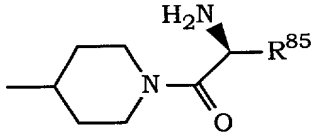
(33) -CN;

(34) a heterocycloalkyl group of the formula



; and

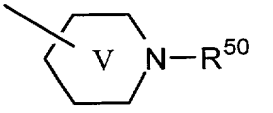
(35) a piperidinyl group of the formula



wherein R^{85} is H, alkyl, or alkyl substituted by -OH or $-SCH_3$; or

R^{20} and R^{21} taken together form a =O group and the remaining R^{46} is as defined above; or

Two of R^{20}, R^{21} and R^{46} taken together form piperidine Ring V

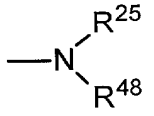


,

wherein R^{50} is as defined above;

with the proviso that R^{46}, R^{20} and R^{21} are selected such that the carbon atom to which they are bound does not contain more than one heteroatom;

R^{44} represents



wherein R^{25} represents heteroaryl, N-methylpiperdinyl or aryl; and R^{48} represents H or alkyl;

Z represents O or S; and

[all the substituents are as defined in Claim 1, and] wherein for the compounds of Formula 5.2 the substituents R^{20}, R^{21}, and R^{46} are selected such that when one of said substituents R^{20}, R^{21}, and R^{46} is selected from the group consisting of: (1) H, (4) -OH, (6) $-NH_2$, (8) $-NHC(O)OR^{22}$, (9) alkyl, (11) phenyl, (17) heteroaryl, (18) hydroxyalkyl, (19) substituted pyridyl, (12) substituted phenyl and (31) -O-alkyl, then the remaining two of said substituents R^{20}, R^{21} and R^{46} cannot both be H when: (a) R^1 and R^2 are both H, and (b) the double bond between C-5 and C-6 is absent, and (c) both A and B are H_2, and (d) R^4 is H, and (e) R^3 is H or Cl at C-8.